

# THE LANCET

## **Supplementary appendix**

This appendix formed part of the original submission and has been peer reviewed.  
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**Thrombolytic removal of intraventricular hemorrhage in treating severe stroke: results of CLEAR III trial, a randomised, multi-center, multi-region, placebo-controlled trial**

**Hanley DF, et al.  
Supplemental Appendix**

**Table of Contents**

1. List of sites, participating investigators and roles.....	2
2. Methods.....	5
2a. Methodological details of the treatment protocol.....	5
2b. Central adjudication of Rankin scale assessments (CARS).....	7
2c. Training, including eGOS and NIHSS .....	9
2d. Severity Index Analysis .....	10
2e. Analysis of Interaction between Age and Mortality .....	11
2f. Summary of Protocol Amendments.....	11
2g. Monte Carlo simulations for sample size calculation .....	13
3. <b>Figures</b> .....	16
3a. Figure S1. CT images correlating to different IVH volumes. ....	16
3b. Figure S2. Effect of treatment on mortality by age.....	17
3c. Figure S3. Relationship between mRS 0-3 and percent clot removed by IVH volume as determined at stability prior to randomization. ....	18
4. <b>Tables</b> .....	19
4a. Table S1. Primary and secondary analyses descriptive listing and corresponding results.....	19
4b. Table S2. eGOS score frequencies for the 30, 180, and 365 day time points. ....	24
4c. Table S3. Univariable and Multivariable Analyses of Dichotomized mRS Modified Rankin Scale (mRS) Score at Day 180 (mRS 0-3 vs. 4-6); Illustrating the Influences of Treatment (alteplase vs. saline), Several Disease Factors, and Effect of Clot Removal on mRS score at Day 180 Outcome.....	24
4d. Table S4. Additional outcome variables by group.....	25
4e. Table S5. Primary reason for exclusion by count and frequency.....	25
4f. Table S6. Demographics for screen failures vs. enrolled subjects. ....	26
4g. Table S7. Proximate causes of death. ....	26
4h. Table S9. Premorbid, historical modified Rankin Scale scores by treatment group.....	27
4i. Table S10. Effect of treatment on mortality by age (data from Figure S4 in tabular format) .....	27
4j. Table S11. Summary of Key Primary and Secondary Analyses and Results from Supplemental Table S1. ....	28
5. <b>REFERENCES</b> .....	29

# 1. List of sites, participating investigators and roles.

Site Name	PI	Lead Neurosurgeon (if not PI)	Study Coordinator	Number of Subjects Enrolled
Rush University	Sayona John	Lorenzo Munoz	Josephine Volgi	25
Chaim Sheba Medical Center	Sagi Harnof		Nina Levhar	24
University of Texas, Houston	George Lopez, Nicole Gonzales	P. Roc Chen	Chad Tremont	21
University of Maryland	E. Francois Aldrich		Charlene Aldrich	19
Johns Hopkins Hospital	Wendy Ziai	Judy Huang	Mirinda White	18
University of Alabama at Birmingham	Mark Harrigan		Lisa Nelson	17
Henry Ford Health System	Panayiotis Varelas	Donald Seyfried	Kathleen Wilson	16
University of Utah	Safdar Ansari	Richard Schmidt	Stephen Chatwin	14
NorthShore Long Island	David LeDoux	Salvatore Insinga	Tim White	13
Thomas Jefferson University Hospital	Jack Jallo		Kara Pigott	13
University of Texas, San Antonio	Jean-Louis Caron		Esther Nanez	13
University of Cincinnati	Opeolu Adeoye	Mario Zuccarello	Lynn Money	12
University of Iowa	Harold Adams	David Hasan	Heena Olalde	12
University of Heidelberg	Julian Bösel	Berk Orakcioglu	Perdita Beck	10
Case-Western Reserve University Hospital	Alan Hoffer		Valerie Cwiklinski	9
Maine Medical Center	David B. Seder	Jeff Florman	Barbara McCrum	9
University of Halle	Katja Wartenberg	Christian Strauss	Doreen Herale	9
University of Pittsburgh Medical Center	Lawrence Wechsler	Paul Gardner	Kara Armbruster	9
Allegheny General Hospital	Ashis H. Tayal	Khaled Aziz	Melissa Tian	8
Stanford University	Chitra Venkatasubramanian	Robert Dodd	Madelleine Garcia	8
UCLA	Paul Vespa		Courtney Real	8
University of Illinois at Chicago	Fernando Testai		Maureen Hillmann	8
University of Mainz	Thomas Kerz	Stefan Welschehold		8
Vall d'Hebron University Hospital, Barcelona	Fuat Arian	Ramon Torne	Lourdes Exposito Mercedes Arrikas	8
Cedars-Sinai Medical Center	Asma Moheet		Felice Lin	7
Hadassah Hebrew University Hospital	Guy Rosenthal		Alex Furmanov	7
Penn State Hershey Medical Center	Kevin Cockroft		Deborah Hoffman	7
University of Buffalo	Jody Leonardo		Linda Bookhagen	7
University of Southampton Hospital	Diederik Bulters		Sophie Marlow Faith Vincent	7
Bellvitge Hospital, Barcelona	Alberto Torres Díaz		Meritxell Santos	6
Columbia University	Sachin Agarwal	E. Sander Connolly	Cristina Falo	6
Sourasky Medical Center Tel Aviv	Nevo Margalit	Erez Nossek	Carmit Ben Harosh	6
University of Alberta	Ken Butcher	Max Findlay	Leka Sivakumar	6
University of South Florida	David Decker	Siverio Agazzi	Denise Fife	6
Georgetown University	Mason Markowski		Courtney Hsieh	5
Hartford Hospital	Inam Kureshi		Sara Jasak	5
Providence Stroke Center	David Antezana	Lisa Yanese	Monica Rodriguez	5

Site Name	PI	Lead Neurosurgeon (if not PI)	Study Coordinator	Number of Subjects Enrolled
Springfield Neurological and Spine Institute	H. Mark Crabtree		Jessica Ratcliff	5
University of Debrecen	Laszlo Csiba	Sandor Szabo	Katalin Szabó	5
University of Leipzig	Dominik Michalski	Juergen Meixensberger	Daniela Urban	5
University of Pecs	Laszlo Szapary	Andras Buki	Peter Csecsei	5
Abington Memorial Hospital	Qaisar A.Shah	Steen J. Barrer	Karin Jonczak	4
Cooper University Hospital	Thomas Mirsen	Alan Turtz	Andrew March	4
Kansas University Medical Center	Paul Camarata		Jason Gorup	4
Mayo Clinic, Jacksonville	William Freeman	Ricardo Hanel	Alexa Richie	4
Medical University of South Carolina	Christos Lazaridis		Marc Lapointe	4
Ohio State University Medical Center	Michel Torbey	Ciaran Powers	Nirav Patel	4
SUNY Upstate Medical Center	Julius Gene Latorre	Eric Deshaies	Iulia Movileanu	4
University of Chicago	Agnieszka Ardelt	Issam Awad	Cedric McKoy	4
University of Tubingen	Sven Poli	Martin Schuhmann	Julia Zeller	4
Virginia Commonwealth University	R. Scott Graham		Kelly Mathern	4
Wake Forest University	Kristi Tucker	John Wilson	Sandra Norona	4
Yale University	David Greer	Murat Gunel	Kimberly Kunze	4
Montreal Neurological Institute at McGill University	David Sinclair		Steven Salomon	3
Mount Sinai	Stanley Tuhim		Ricardo Renvill	3
Temple University Hospital	Michael Weaver		Carol Von Hofen / Kathleen Hatala	3
University of Erlangen	Hagen Huttner	Oliver Ganslandt	Anja Schmidt	3
University of Szeged	Pal Barzo	Zoltán Mencser	Eniko Fako	3
University of Texas, Southwestern, Dallas	Christiana Hall	Christopher Madden	Katrina Van De Bruinhorst	3
Vanderbilt	Michael Froehler	J Mocco	Emily Gilchrist	3
Hospital Sao Paulo Universidade Federal de Sao Paulo/UNIFESP	Gisele Sampaio Silva	Italo Caprano Suriano	Dirceu Regis, Raul Valiente	2
Hospital de Clinicas de Ribeirao Preto	Pedro Telles Cougo Pinto	Benedito Oscar Colli	Rodrigo Barbosa Cerantola	2
Hospital de la Santa Creu i Sant Pau, Barcelona	Joan Marti-Fabregas	Fernando Munoz	Rebeca Marin Bueno	2
Medical College of Wisconsin	Ann Helms	Wade Mueller	Alicia Constanquay	2
Saint Louis University	Salvador Cruz-Flores	Saleem Abdulrauf	Susan Eller	2
U Hosp, Inselspital, Bern	Michael Reinert		Ralph Schaer	2
University of Zurich	Andreas Luft	Betrand Actor	Benjamin Hertler	2
Mercy General Sacramento	Kavian Shahi		Susan Croopnick	1
New Jersey Neuroscience Institute at JFK	Martin Gizzi		Charles Porbeni	1
Newcastle General Hospital	A D Mendelow	Prokopios Panaretos, Francesco Vergani	Barbara Gregson	1
NorthShore Chicago	Issam Awad		Jen Jaffe	1
St. Luke's Brain and Stroke Institute, Kansas City	Darren Lovick		Bridget Brion	1
University of Southern California - Keck School of Medicine	Benjamin Emanuel	William Mack	Doris Arroyo	1
Albert Einstein Medical Center	George Newman	Mark Kotapka	Nwosu Chukwunweike John	0
Atlantic Neuroscience Institute	Igor Ugorec		Zenona Lesko	0
Boston University Medical Center	James Holsapple		Thai Q. Vu	0

Site Name	PI	Lead Neurosurgeon (if not PI)	Study Coordinator	Number of Subjects Enrolled
Budapest - Honved Korhaz	Peter Bazso		Attila Josvai	0
Charite Universitatsmedizin in Berlin	Eric Juttler			0
Duke University Medical Center	Michael Luke James		Ellen Bennett	0
Hospital Sao Jose, Joinville	Alexandre Luiz Longo	Andre Sanches Pitzschk	Juliana Antunes Safanelli	0
Hospital Universitario Clementino Fraga Filho	Jorge Marcondes de Souza		Marco Oliveira Py	0
Hospital de Clinicas de Porto Alegre	Sheila Cristina Ouriques Martins	Apio C. Martins Antunes	Natacha Fleck	0
Hospital de Pronto Socorro de Porto Alegre	Marcelo Kern	Rogerrio Symanski da Cunha	Susana Maria Endres	0
InterCoastal Medical Center	Mauricio Concha	Robert Knego	Jeanette Bryant	0
London University Health Sciences Centre	Mel Boulton		Robert Mayer	0
Loyola University Medical Center	Michael Schneck	Hazem M. Ahmed	Linda Chadwick	0
Massachusetts General Hospital	Christopher Ogilvy		Michael T Phillips	0
Mayo Clinic Arizona	Maria Aguilar	Richard Zimmerman	Patricia O'Donnell	0
Puerto Rico Medical Center	Fernando Santiago	Ricardo Brau	Ingrid Rodriguez	0
Rambam Medical Center	Menashe Zaaroor	Leon Levi	Efrat Velblum	0
Ruan Neurology Clinic and Research Center	Michael Jacoby	Robert Hirschl	Sheryl Inman	0
Salford Royal NHS Foundation Trust	Hiren Patel	John Kitchton	Victoria OLoughlin	0
Swedish Medical Center	David Newell		Jeannie Steed	0

## 2. Methods

### 2a. Methodological details of the treatment protocol

#### Eligibility Criteria:

#### Inclusion Criteria

1. Age 18-80.
2. Symptom onset less than 24 hrs prior to diagnostic CT scan.
3. Spontaneous ICH  $\leq 30$  cc and IVH obstructing 3<sup>rd</sup> and/or 4<sup>th</sup> ventricles.
4. ICH clot stability: ICH must be  $\leq 30$  cc on initial presentation and not exceed 35 cc on subsequent pre-randomization stability scans. A CT scan performed 6 hours or more after IVC placement must be stable (difference is  $\leq 5$  cc) compared to the most previous CT scan as determined by the (AxBxC)/2 method.  
 Temporary Criterion: If the clot is not stable (i.e., difference is  $> 5$  cc), a repeat CT scan must be performed at least 12 hours later and compared to the most previous CT scan. Investigator may continue to screen every 12 hours up to 72 hours for the initial bleeding to stabilize, as long as the subject is able to be randomized within 72 hours of time of diagnostic CT scan and the clot remains  $\leq 35$  cc. If the size stabilizes (i.e., enlargement  $\leq 5$  cc between 2 sequential CT scans) and remains  $\leq 35$  cc, the patient is eligible.
5. IVH clot stability: The width of the lateral ventricle most compromised by blood clot must not increase by  $> 2$  mm, allowing for movement of blood under influence of gravity.  
 Temporary Criterion: If the clot is not stable (i.e., difference is  $> 2$  mm), a repeat CT scan must be performed at least 12 hours later and compared to the most previous CT scan. Investigator may continue to screen up to 72 hours for the initial bleeding to stabilize, as long as the subject is able to be randomized within 72 hours of time of diagnostic CT scan. If the size stabilizes (i.e., enlargement  $\leq 2$  mm between 2 sequential CT scans), the patient is eligible.
6. Catheter tract bleeding must be less than or equal to 5 cc on CT scan for stability.  
 Temporary criterion: If a catheter tract hemorrhage is present on the CT scan done 6 hours after IVC placement and is  $> 5$  cc or  $> 5$  mm, obtain a repeat CT scan 12 hours later. This includes any bleeding at the entry site or along the catheter tract that is 5 mm in diameter seen on any CT slice or is 5 mL on more than one CT slice. If the catheter tract hemorrhage further enlarges by  $> 5$  cc or  $> 5$  mm as compared to the most previous CT scan, the investigator may continue to screen by repeat CT scan every 12 hours for the bleeding to stabilize, as long as the subject is able to be randomized within 72 hours of time of diagnostic CT scan. If the size stabilizes (i.e., enlargement  $\leq 5$  cc or  $\leq 5$  mm between 2 sequential CT scans), the patient is eligible.
7. On stability CT scan, the 3<sup>rd</sup> and/or 4<sup>th</sup> ventricles are occluded with blood.
8. All patients randomized will have had EVD placed, ideally using no more than 2 complete passes (including "soft passes" using the original trajectory), on an emergent basis as defined by the "standard of care" neurosurgical/critical care decisions of the managing physicians. If more than 2 passes are required for placement, additional stabilization of IVC site will be determined with a CT performed at 24 hours after IVC placement.  
 Temporary criterion: If no IVC is in place at the time the patient is initially screened, the decision to place an IVC may occur after the patient is initially screened but an IVC must be in-place and stable at the time of randomization.
9. Patients with primary IVH are eligible (i.e. with ICH=0).
10. SBP  $< 200$  mmHg sustained for the 6 h before drug administration (closest to randomization).  
 Temporary criterion: Blood pressure inclusion criteria not met when the patient is screened: Most vital signs are stabilized within the time window for enrollment.
11. No test article may be administered until at least 12 hours after symptom onset.
12. Able to randomize within 72 h of CT scan diagnosing IVH (provided the time of symptom onset to diagnostic CT does not exceed 24 h).  
 Temporary criterion: The 72 hour limit may be extended with approval from the Coordinating Center to allow for clot stability (ICH, IVH, catheter tract), INR stability, or other valid reason.
13. Historical Rankin of 0 or 1.

#### Exclusion Criteria

1. Suspected (unless ruled out by angiogram or MRA/MRI) or untreated ruptured cerebral aneurysm, ruptured intracranial AVM, or tumor. Treatment of an existing aneurysm or AVM must have occurred at least 3 months before the current onset.

Temporary criterion: This is especially important in primary IVH, when no ICH source is found. CT angiogram, angiogram, MRA/MRI, or general diagnostic study (prior to confirming patient eligibility in the protocol) is standard of care to rule out underlying etiology. If the CT angiogram, angiogram or MRA/MRI is negative, the patient is eligible. The PI must document rationale if imaging is not done.

2. Presence of a choroid plexus vascular malformation or Moyamoya disease.
3. Clotting disorders. Subjects requiring long-term anti-coagulation are excluded.  
 Temporary criterion: Reversing anticoagulation will be permitted where long-term anticoagulation is not required.
4. Use of Dabigatran, Apixaban, and/or Rivaroxaban (or a medication from the same medication class) prior to symptom onset.
5. Platelet count < 100,000, INR > 1.4.  
 Temporary criterion: Low platelet counts etc. on admission can normalize within 24 hours as can an INR normalize to  $\leq 1.4$ .
6. Pregnancy (positive serum or urine pregnancy test).
7. Infratentorial hemorrhage
8. Thalamic bleeds with apparent midbrain extension with third nerve palsy or dilated and non-reactive pupils. Other (supranuclear) gaze abnormalities are not an exclusion. Note: Patients with a posterior fossa ICH or cerebellar hematomas are ineligible.
9. SAH at clinical presentation (an angiogram (angiogram, CTA, MRA/MRI) must be obtained when the diagnostic CT scan shows SAH or any hematoma location or appearance not strongly associated with hypertension. If the angiogram or other imaging does not detect a bleeding source to account for the hemorrhage, the patient is eligible for the study.) Subsequent appearance of cortical SAH secondary to clot lysis is not a dosing endpoint.  
 Temporary criterion: An angiogram must be obtained when the diagnostic CT scan demonstrates subarachnoid hemorrhage or any hematoma location suggestive of aneurysm or appearing not strongly associated with hypertension. If the angiogram/imaging does not demonstrate a bleeding source that accounts for the hemorrhage, the patient is eligible for the study.
10. ICH/IVH enlargement that cannot be stabilized in the treatment time window.  
 Temporary criterion: ICH enlargement during the 6-hour stabilization period (6 hours after IVC placement): It is permitted to screen up to 72 hours after diagnostic scan. If the ICH clot size stabilizes (i.e., enlarges no more than 5 cc) and does not exceed 35 cc (an ICH clot size of 35 cc allows for stabilization of a 5cc expansion for those patients at the upper limit of the ICH clot size limit), the patient is eligible.
11. Ongoing internal bleeding, involving retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts. (Patient with prior bleeding that is clinically stable for 12 h or more without any coagulopathy or bleeding disorder is eligible).
12. Multi-focal, superficial bleeding, observed at multiple vascular puncture and access sites (e.g., venous cutdowns, arterial punctures) or site of recent surgical intervention.
13. Prior enrollment in the study.
14. Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated. Subjects who are not expected to survive to the day 180 visit due to co-morbidities and/or are DNR/DNI status prior to randomization are excluded.  
 Temporary criterion: Although these situations are often irreversible, under other conditions, change can occur over 24 hours.
15. Planned or simultaneous participation (between screening and Day-30) in another interventional medical investigation or clinical trial. Patients involved in observational, natural history, and/or epidemiological studies not involving an intervention are eligible.
16. No subject or legal representative to give written informed consent.

**Stability Protocol:** The risks of initial hematoma growth/instability were managed by use of a stability protocol combining normalization of coagulation parameters, blood pressure (BP) management, and repeat CT assessment of clot size measured using the ABC/2 method.<sup>1</sup> Six or more hours after the diagnostic CT, a stability CT was performed to ensure that the ICH clot was not expanding by >5 mL and that qualitative expansion in IVH had not occurred, providing image demonstration of a safe starting point for clot reduction therapy, defined as the absence of ongoing bleeding before randomization and initiation of test article. The CT could be repeated every six hours until the clot stabilized or just before the 72-hour eligibility window closed, whichever came first. In addition, a magnetic resonance image (MRI) or CT angiography (CTA) was encouraged as vascular pathology screening; an angiogram was encouraged where equivocal findings were noted on vascular pathology screening.<sup>2</sup> An INR  $\leq 1.4$ , a platelet count > 100,000, and BP stability < 200 mm Hg were required prior to randomization.<sup>3,4</sup>

**EVD management:** The Surgical Center located at the University of Chicago actively reviewed all catheter placements and monitored clot removal assessments, catheter discontinuation protocols, and evaluated the safety and efficacy of the surgical procedure.<sup>1</sup> The Surgical Center recommended pull-back and/or replacement of catheters that were sub-optimally placed within the

ventricular system as well as placement of a second, concurrent catheter ipsilateral or contralateral to the most affected side for optimal test article delivery. Recommendations were not mandatory.

**Test article administration protocol:** Eligible subjects were adaptively randomized to receive intraventricular injections of either normal saline or alteplase. Local pharmacists were notified to prepare the assigned “test article” such that the clinicians remained blind to assignment. Intraventricular alteplase administrations of 1.0 mg in 1 mL were given every 8 hours, up to 12 doses, or until an endpoint was reached. All doses were followed by a 3 mL flush of preservative-free normal saline. After each assigned dose, the system was closed for one hour to allow drug-clot interaction, and then opened to allow for gravitational drainage. Trial-defined clinical endpoints included, opening of 3<sup>rd</sup> and 4<sup>th</sup> ventricles, mitigation of IVH-related mass effect, 80% reduction of clot volume measured on the stability CT, reaching a maximum of 12 doses or occurrence of a clinically significant bleeding event, defined as a clot enlargement accompanied by sustained drop of more than two points on the Glasgow Coma Scale (GCS) motor score with CT-demonstrated ICH enlargement. CT scans were subsequently obtained every 24 hours until dosing was complete to evaluate safety and drainage. Test article administration was performed under standard conditions to maintain sterile environment and cranial compartment euolemia. Procedural training was mandatory. Selection of the dosing endpoint was determined on a subject-by-subject basis at each site.

**Image analysis:** To optimize accuracy and minimize investigator bias, clot volumes were analyzed by a core laboratory utilizing semi-automated segmentation and Hounsfield thresholds.<sup>5</sup> This was performed using OsiriX software (v.4.1, Pixmeo; Geneva, Switzerland) on DICOM images of each subject’s stability and treatment scans. This approach has been validated for accuracy and inter-rater reliability.<sup>6</sup> Core lab values were utilized in all analyses. Core lab defined location as either thalamus or other (lobar, putamen, caudate).

**Prohibited medications:** The administration via any brain catheter of any thrombolytic agent (other than the study agent administered per protocol) was prohibited. Clogged catheters were flushed with normal saline. Antithrombotic and antiplatelet agents were prohibited prior to the day 30 follow-up visit. Enoxaparin at therapeutic doses  $\geq 1.0$  mg/kg subcutaneously every 12 hours was prohibited during the 12-month study period following randomization.

## **2b. Central adjudication of Rankin scale assessments (CARS)**

### **CARS Infrastructure**

The Central Adjudication of Rankin Scale assessments (CARS) system is a secure web based portal designed specifically for the upload and central adjudication of video recorded mRS endpoints in the CLEAR-III trial (<https://www.glasgowctu.org/CLEAR3>). The CARS portal was developed by staff of the Institute of Cardiovascular and Medical Sciences and technical support of the Robertson Centre for Biostatistics, both within the University of Glasgow. It provides fully validated backend study databases for collection of all Rankin scores and review decisions taken from endpoint committee members, where applicable.

The CARS systems are fully documented and incorporate a complete audit trail from upload to score. CARS is fully compliant with relevant GCP guidelines and was developed and validated in accordance with Computerised Systems for Clinical Research guidelines and 21 CFR Part 11 – Electronic Records and Electronic Signatures. Dates and times are recorded at both local and central database levels and are compliant with ISO 8601: 1988 (E) (Data elements and interchange formats – Information interchange – Representation of dates and times). The web pages are only accessible using secure socket layer (SSL) communication, which utilises a validation certificate created for a particular server within a specific domain. This enables authentication from the server to the user’s browser and encrypts all traffic between their local computer and the authenticated host server. The web server is secured by VeriSign, the BT Trust Services Global Server Certificate program and is firewall-protected.

**Training in Modified Rankin Scale Assessment:** All CLEAR-III assessors (local and central) underwent training and certification in mRS assessment using an online training resource. Study staff were also provided with bespoke instruction for use of the CARS system in the trial, including guidance on mRS scoring and on conducting interviews for central review.

**CARS Staff:** The CARS system was overseen by a team at the University of Glasgow comprising an outcomes manager who oversaw the day to day running of the system, trained and experienced adjudicators, and a team of translators for relevant non-English languages.

**Communication between CARS System and Trial Management Systems:** The CARS portal was integrated with the CLEAR-III EDC managed by VISION during initial trial set up, such that investigators were able to upload assessments via the main trial management system in a secure manner. This simultaneously automated transfer of information (such as patient identification number, visit date, visit site and assessment language) to the CARS system. The same connection allowed the CARS system to return status

reports including 'successful upload' to the trial management system and ultimately to return the completed mRS score. Automated status updates were relayed to both the trial management system and the CARS team both on attempt and on completion of upload, to allow monitoring of video uploads and quick identification of any problem. All communications maintained blinding of the CLEAR-III coordinating center staff.

**Addressing Technical difficulties:** A technical support team based at the Robertson Centre of Biostatistics within the University of Glasgow was responsible for the maintenance of the CARS portal and responding to any issues that arose. Team members were available via telephone or email.

### **Performing and Uploading Modified Rankin Scale Assessments**

**Recording of the Modified Rankin Scale Assessment:** A portable digital video camera with an in-built microphone was used to record the mRS interview. Video cameras were supplied through the CLEAR-III management team. Examples of models used are the FLIP Mino (CISCO systems, San Jose US) and the PIXPRO SPZ1 (Eastman Kodak Company, Rochester US). The assessor was directed to sit opposite the participant and beside (or holding) the camera, out of view. The camera was to be positioned a suitable distance from the participant so that the recording captured the participant's face and trunk. The videos were recorded in standard definition at 60fps ensuring a reasonable file size for upload. The CARS system handled a diverse range of commonly used file types such as .mp4, .wmv, .avi, .mov, .mpg, .mts and .m4v.

**Upload of the Modified Rankin Scale Assessment:** Upload was performed via the trial management system (VISION EDC), requiring trial staff only to have a single log in. The USB connections were used to connect the camera to a computer and to transfer files for upload. Users monitored progress of the upload via a status bar and received an automated notification upon successful upload.

### **Central Adjudication of Modified Rankin Scale Assessments**

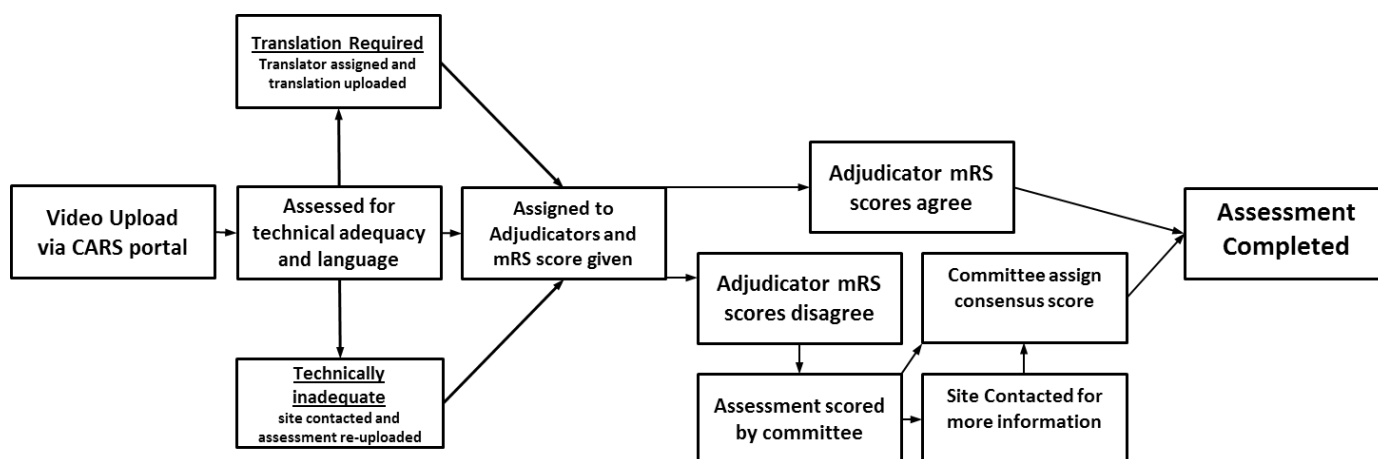
**Initial Review for Technical Adequacy, Anonymity and Masking of Treatment Allocation:** In the CLEAR-III trial an outcomes manager received an automated email upon successful upload of an assessment. The system would then block further upload of assessments for this participant. Upon receipt of successful upload notification, the outcomes manager reviewed the assessment for quality and maintenance of blinding. If the assessment was clearly inadequate, either in terms of technical factors (such as no audio, no patient visible, incorrect patient study identity or visit number) or was lacking in sufficient information to begin the scoring process, it was labelled with a status of 'technically inadequate.' This would prompt an automated message to the local investigator that further information or a replacement assessment was required. The CARS system would update the EDC and then allow further uploads to be submitted. Minor editing of assessments could be performed by the outcomes manager at this stage to preserve anonymity, masking of treatment allocation or to conceal details of the local score; such editing was tracked for audit purposes.

**Translation of Non-English Language Clips:** Non-English language assessments were sent for translation to a bilingual native speaker of that language, with experience in the use of the mRS. Translations were performed using a digital recording device and the ensuing audio file was uploaded directly to the CARS system, where the audio file was then merged (overdubbed) with the original video of the mRS assessment. Both the native language and translated assessment were available for review by the assigned adjudicators. Upon successful upload of a translation the outcomes manager again assessed the translations to ensure blinding and protection of patient confidentiality.

### **Review and Scoring of Assessments**

Assessments were assigned to CARS reviewers, who would be contacted via an automated email containing a direct link to the assigned assessment in the CARS system. Reviewers each had unique login details to permit tracking of workload and quality. They could access the video clips via either desktop or portable devices, to allow timely review and scoring. Reviewers recorded their chosen score within the CARS portal while the relevant video recording was on screen, and were also asked to record comments to justify their choice of score, that would be helpful in the event of subsequent committee discussion.

In the CLEAR-III trial, the scoring algorithm accepted as final any score that agreed between the local and first central rater. However, if there was a discrepancy between the local and first CARS score, then the assessment proceeded to committee review, for which 3 further independent reviews of this assessment were performed. Once 4 scores had been independently assigned, the committee of these raters discussed the assessment and reached a consensus on final score. This consensus score was entered to the CARS portal by the committee chairman and the score was automatically returned to the VISION EDC. Tracking of the stages is possible.



### **Quality Control and Ongoing Training**

We monitored inter-rater agreement for mRS scores, allowing us to optimize assessment guidance or to identify any rater who may benefit from additional training. We provided feedback to investigators at all sites and arranged refresher training in mRS assessment during the CLEAR-III trial via webinar sessions, including example video assessments.

### **CARS staff**

#### **Adjudicators:**

Jen Alexander (Queen Elizabeth University Hospital Glasgow, UK), Jesse Dawson (University of Glasgow, UK), Peter Higgins (University of Glasgow, UK), Kennedy Lees (University of Glasgow, UK), Kate McArthur (University of Glasgow, UK), Terry Quinn (University of Glasgow, UK), Matthew Walters (University of Glasgow, UK), Alastair Wilson (University of Glasgow, UK)

#### **Translators:**

Sukainah Al Alshaikh (University of Glasgow, UK), Samantha Alvarez-Madrado (University of Glasgow, UK), Péter Bukovics (University of Pecs, Hungary), Laila Day (University of Glasgow, UK), Catarina Fonseca (Universidade de Lisboa, Portugal), Benedikt Frank (University Hospital Essen, Germany), Nora Gonzalez (University of Glasgow, UK), Karim Hajjar (University Hospital Essen, Germany), Kerrick Hesse (University of Glasgow, UK), Nicki Karlen (Emissary LLC, Israel), Kitti Kovacs (University of Debrecen, Hungary), Ananada Mirchindani (University of Glasgow, UK), Guillaume Turc (Sainte-Anne Hospital Paris, France)

### **ACKNOWLEDGEMENTS**

We thank all the outcomes assessors and translators who work across our various trials. The initial CARS studies were funded by a grant from the Chief Scientist Office Scotland (CZB/4/595).

### **2c. Training, including eGOS and NIHSS**

Training modules were prepared for key personnel at the enrolling sites. Key personnel were defined as the principal investigator, coordinator, pharmacist and others designated to perform data collection, drug preparation, and drug administration.

Initial Training ensured that all site personnel were properly trained concerning FDA regulations, ICH guidelines, and trial policies and procedures. During the investigator start up meeting, the first training module included design and methods of the trial, the importance of integrity in acute and follow-up data collection, the need for data security, study organization, performance and compliance, and actual treatment procedures, and coordinators were required to work through sample VISION/Prelude EDC screens. The training modules were incorporated into the MOP. The CC worked with the site investigators to continuously identify and correct problems of compliance, data collection, outcomes assessment and data processing.

The following is the list of mandatory investigator/coordinator training modules:

Enrolling Site Training Events – New Personnel	Method	Site Initiation	Annual Recertification	Refresher
Design and methods of the trial Importance of integrity in data collection Need for data security Study organization Performance and compliance Treatment procedures Current Study Results	Power point presentation	✓		✓
Human Subjects HIPAA Ethics Conflicts of Interest	On-line training	✓		
Electronic Data Entry	On-line training	✓		
Sample Data Set	Hands on training	✓		
Web Site Access	On-line training	✓		
Modified Rankin Scale Certification	Video training and test	✓	✓	
NIHSS Certification ←	Video training and test	✓	✓	
eGOS, SIS, EQ, QOL, PBSI ←	Power point presentation	✓		
CT Stability Training	On-line training and certification	✓		✓
Drug Administration Certification	Video training and test	✓		
IVC Placement Certification	Power point presentation	✓		
Graeb Scoring Tutorial	Power-point presentation	✓		
Ventricular Opening Endpoints	Power-point presentation	✓		
Pharmacy Procedures	Power-point presentation	✓		
Recruitment and Consent	Power-point presentation	✓		
AE and SAE Reporting	Power-point presentation	✓		
Protocol Deviations	Power-point presentation	✓		
Study Progress and Procedural Changes	Power-point presentation	✓		
Protocol Test	Web-based Certification test	✓	✓	

Extended GOS (eGOS): Site personnel were trained on eGOS administration technique using a MS PowerPoint module developed by the CC. The eGOS was obtained by local, trained personnel as part of the follow-up procedures at days 30, 180, and 365. Proxy interview was utilized if the subject scored <18 on the Mini-Mental Status Examination. The eGOS was first recorded onto a paper bedside worksheet as source documentation and then entered into the VISION EDC system. These date were monitored by the QA Monitor for transcription errors and consistency among all other outcomes assessments.

NIHSS: Site personnel were instructed to utilize existing online NIHSS certification websites to obtain certification and then upload documentation of successful course completion to the VISION EDC electronic master file. Certification was obtained prior to the site initiation meeting with recertification required annually. NIHSS was captured if done by the clinical care team as close to the time of presentation as possible, and then done by a certified examiner at randomization, day 7, and again at follow-up days 30, 180, and 365. The NIHSS was the only outcomes assessment done at day 7. The interview was first recorded onto a paper bedside worksheet as source documentation and then entered into the VISION EDC system. These date were monitored by the QA Monitor for transcription errors and consistency among all other outcomes assessments.

## 2d. Severity Index Analysis

As an initial step in developing our severity index for predicting mRS (0-3), categories for well established “explanatory” variables: age, GCS at randomization, and stability ICH were created according to the distribution of the data for each variable. Two or more categories were combined if equally predictive of mRS (0-3), based on univariate logistic regression models. IVH and ICH location were set to their pre-specified values (i.e., < 20 mL, >= 20 – 50 mL, and > 50 mL, and thalamic and non-thalamic, respectively). The final categories considered were: Age (<=50 yrs, 50- <60 yrs, 60 – <65 yrs, 65 - <70 yrs, and >=70 yrs), GCS (<= 9, 10-12, and 13-15), ICH (<= 8 mL, >8 – 15 mL, > 15 mL), IVH (< 20 mL, >=20 – 50 mL, > 50 mL), and ICH location (thalamic, non-thalamic). Next, a multivariable logistic regression was created that regressed the binary outcome of mRS <=3 vs. mRS >3 on these 5 predictors. (Gender was considered in this model, but was determined to be non-significant, and therefore dropped).

Based on the coefficients of this model, the severity was created that weighed each category as follows: Severity Index = 1.0 \*(1 if age >=50 and <60, 0 otherwise) + 1.3\*(1 if age >=60 and <65, 0 otherwise) + 1.85\*(1 if age >=65 and <70, 0 otherwise) + 2.0\*(1 if age >=70, 0 otherwise) + 1.7\*(1 if GCS <=9, 0 otherwise) + 1.0\*(1 if GCS =10-12, 0 otherwise) + 0.8\*(1 if thalamic, 0 otherwise) + 0.8\*(1 if IVH >=20 and <=50, 0 otherwise) + 2.4\*(1 if IVH >50, 0 otherwise) + 0.85\*(1 if ICH >8 and <=15, 0 otherwise) + 2.0\*(1 if

ICH >15, 0 otherwise). This score gives a maximum possible value of 9.0; however the highest score seen in the data set was 8.85. A score of 0 indicates the lowest severity (e.g., a patient with an age ≤50 years, GCS ≥13, IVH < 20 mL, ICH ≤8 mL and non-thalamic ICH).

Regression of the odds of mRS (0-3) gives a decrease of approximately 63% in the odds of having a 180-day mRS ≤3 for each one unit increase in the severity score, a result that is highly statistically significant (OR [95% CI] = 0.37 [0.31, 0.44],  $p < 0.0001$ ). Treatment assignment was not statistically significant once we controlled for severity by this index, a result that is consistent with that reported in Table S2 (Adj OR [95% CI] = 0.91 [0.58, 1.43],  $p = 0.690$ ). In addition, there was no evidence of a treatment by severity interaction effect ( $p=0.971$ ).

However, clot removal as measured by normalized AUC (as a percent of stability IVH), was significant once we controlled for severity (Adj OR [95% CI] = 0.998 [0.997, 1.000],  $p = 0.040$ ). Again there was no evidence of an AUC by severity interaction effect ( $p=0.773$ ).

A similar process was followed to create an index score to predict 180-day mortality. Categories of variables were slightly different than for the mRS (0-3) index, and thalamic location was not found to be predictive of mortality as compared to other ICH locations. The mortality score was created as follows: Mortality Index =  $0.5 \times (1 \text{ if age } \geq 50 \text{ and } < 60, 0 \text{ otherwise}) + 0.6 \times (1 \text{ if age } \geq 60 \text{ and } < 65, 0 \text{ otherwise}) + 1.0 \times (1 \text{ if age } \geq 65 \text{ and } < 70, 0 \text{ otherwise}) + 1.4 \times (1 \text{ if age } \geq 70, 0 \text{ otherwise}) + 0.8 \times (1 \text{ if GCS } \leq 7, 0 \text{ otherwise}) + 1.0 \times (1 \text{ if IVH } \geq 20 \text{ and } \leq 50, 0 \text{ otherwise}) + 1.7 \times (1 \text{ if IVH } > 50, 0 \text{ otherwise}) + 0.9 \times (1 \text{ if ICH } > 15, 0 \text{ otherwise})$ . This score gives a maximum possible value of 4.8, with the highest value seen in the data set of 4.8.

Regression of the odds of death at 180 days indicates just over a two-and-half fold increase in the odds of death for each one unit increase in the mortality score, a result that is highly statistically significant (OR [95% CI] = 2.74 [2.13, 3.53],  $p < 0.0001$ ). Treatment assignment was highly statistically significant once we controlled for the mortality index, a result that is consistent with our reported survival analyses (Adj OR [95% CI] = 2.01 [1.26, 3.20],  $p = 0.003$ , severity adjusted odds of death at 180 days for saline vs. alteplase). This effect was consistent across all levels of the mortality severity index.

## 2e. Analysis of Interaction between Age and Mortality

As shown in Figure S3 and Table S10, analyses of the interaction between age and mortality lend weight to our conclusion that alteplase reduces 180-day mortality compared to the saline-treated patients.

In our assessment of this possible interaction on mortality, we considered 1) the risk ratio (RR) of death across 5 strata of age (<50 yr, 50 - <60 yr, 60 - <65 yr, 65 - <70 yr, and >70 yr), and 2) created a Cox model that incorporated an age (continuous variable) by treatment interaction.

We found that the RR varied from 0.42 – 0.80 across all five age strata, giving a Mantel-Haenszel combined RR = 0.64. We then tested the null hypothesis for homogeneity across age strata ( $\chi^2 [\text{deg} = 4] = 1.41, p = 0.842$ ), the non-significant finding is concordant with the presence of consistent relative risk across all age strata (e.g. no heterogeneity of treatment effect across age strata). Similarly, the age by treatment interaction term in the Cox model with both the main effects of age and treatment is not statistically significant (HR interaction = 1.01,  $p = 0.665$ ). This suggests the effect of alteplase on mortality is not modified by age.

Therefore, based on these analyses, we concluded that the difference in mortality between treatment arms is consistent across every age strata, and there is no statistical evidence indicating an effect modification of age on the association between treatment and mortality.

## 2f. Summary of Protocol Amendments

### v1.1 (8 Oct 2008) to v2.0 (15 Jun 2009)

- Vital signs monitoring/data collection frequency changed from q1hr to q4hr. Vital signs monitoring/data collection schedule changed from days 1 through ICU discharge to days 1-7 with daily assessment of ICP management beginning on day 8 and continuing through IVC removal. ICP management data will be collected retrospectively at hospital discharge and will be used to monitor compliance with EVD management/weaning protocol.
- Removed the GOS scale as an outcome scale. The GOS will now be computed from the extended GOS.

- Added the EQ-5D to the day 90 and 270 telephone follow-up visits.
- The Mini-Mental State Exam will now be administered to everyone, not just to subjects with GCS<15 as previously written.
- Exclusion criteria:
  - Added Moyamoya disease.
  - Lowered the acceptable INR from 1.7 to 1.3 for eligibility and for dosing. Also deleted PT as a determination of eligibility. Eligibility is now based on INR  $\leq$  1.3 and aPTT within normal limits.
- Deleted daily laboratory assessments of PT, fibrinogen, plasminogen, d-dimer. Now only collecting daily serum WBC, Hct, platelet count, INR, aPTT as well as daily CSF labs. Plasminogen and fibrinogen will be assessed once prior to first dose.
- Deleted IVC tip culture upon removal.
- Specified that all quality monitoring of subject data will be done remotely. The VISION/Prelude EDC system will be used to query the data. Source documentation may remain identified.

#### **V2.0 (15 Jun 2009) to v3.0 (22 Mar 2011)**

- Incorporated adaptive randomization.
- Added the Personal Health Utility Assessment Interview to the 180 day follow-up visit.
- Inclusion criteria:
  - Changed the enrollment window from first dose within 72 hours of diagnostic CT to randomization within 72 hours of diagnostic CT.
  - Raised the acceptable INR from 1.3 to 1.4.
- Permit use of heparin during the acute treatment period.
- Increased stability period from 12 to 24 hours during dosing.

#### **V3.0 (22 Mar 2011) to v4.1 (17 Apr 2013)**

- Added exclusion of patients taking Dabigatran.
- Allow the use of enoxaparin during dosing along with other low molecular weight heparins that are already considered Permitted Interventions.

#### **V4.1 (17 Apr 2013) to v4.2 (1 Jul 2013)**

- Added further exclusion from randomization of patients taking Apixaban, Rivaroxaban and similar medications in addition to Dabigatran.
- Added prohibition of Apixaban and Rivaroxaban in addition to Dabigatran through day 30.

## 2g. Monte Carlo simulations for sample size calculation

Power and sample size derivations are based on the 180-day outcomes, to yield minimum statistical power calculations. That is, the given sample size will have at least the reported power to observe a treatment difference at 180 days. Inclusion of additional data and information through the longitudinal analyses will serve to enhance model efficiency and thus increase power.

**2g.1. Statistical Power - Primary Endpoint 1 (Modified Rankin Scale  $\leq 3$  at 180 days).** Statistical power for primary endpoint 1 is derived from Monte Carlo simulation studies based on the empirical relationships observed in the previous Safety, CLEAR A and CLEAR B studies. mRS outcomes are simulated from sequential conditional distributions based on the previously observed data in the Safety, CLEAR part A, and CLEAR part B (24 patients) studies as follows:

$$\begin{aligned} F(\text{mRS, site, rt\_PA, IVH volume, ICH volume, ICH Clot Location}) \\ = F(\text{mRS} \mid \text{site, rt\_PA, ivh\_10cc, ich\_10cc, location}) \\ * F(\text{rt\_PA} \mid \text{ivh\_10cc, ich\_10cc, location}) \\ * F(\text{ivh\_10cc} \mid \text{ich\_10cc, location}) \\ * F(\text{ich\_10cc} \mid \text{location}) \\ * F(\text{location}) \end{aligned}$$

Simulation data for power calculations is thus generated in five steps:

**Step 1: Simulate clot locations.** Clot locations in the 88 patients from the Safety, CLEAR part A and part B studies were distributed as: Thalamus, n=41 (47%); Caudate/Putamen, n= 16 (18%), Other location, n=10 (11%), No Measurable Clot, n=21 (24%). We use this information to guide clot locations in a simulated sample of size N=500 by drawing from a multinomial distribution with related probabilities. For example, in simulation dataset 1, we drew clot locations of: Thalamus, n=246 (49%); Caudate/Putamen, n= 134 (27%), Other location, n=57 (11%), No Measurable Clot, n=63 (13%).

**Step 2: Simulate ICH volumes based on clot location.** ICH volumes within the “No Measurable Clot” location are all 0cc. For the remaining clot locations, lognormal distributions of ICH volumes truncated at 30cc were used to account for design restrictions and skewness in the observed Safety, CLEAR A and CLEAR B ICH volumes. Calculated lognormal parameters (mean, standard deviation) were: Thalamus, (2.56, 0.73); Caudate/Putamen, (2.16, 0.86), other location, (1.42, 1.06). For our (N=500) simulation dataset 1, the resulting joint distribution of clot locations and ICH volumes is depicted in Figure 2g-1.

**Step 3: Simulate IVH volumes based on ICH and clot location.** In the Thalamus location, a linear regression of IVH volume on ICH volume with estimated relationship  $E(\text{IVH}) = 23.81 + 0.45(\text{ICH})$ , and residual standard deviation of 20.35 fit the data well. For the Caudate/Putamen location, a linear regression of IVH volume on ICH volume with estimated relationship  $E(\text{IVH}) = 57.51 + 0.15(\text{ICH})$  and residual standard deviation of 39.48 was used. For the Other location, the IVH-ICH relationship was inverse, with parameter estimates of  $E(\text{IVH}) = 49.84 - 0.83(\text{ICH})$  and residual standard deviation of 22.34. In the “No Measurable Clot” location, there was no information to estimate an IVH-ICH relationship, and thus IVH volume was simulated under a Gaussian model using the observed sample mean and standard deviation values of (mn=68.76, sd=37.79). Joint plots of the IVH volume, ICH volume, and clot location relationships are shown in Figure 2g-2.

**Step 4: Simulate the rt-PA assignment based on IVH & ICH volumes, and clot location.** The current study design incorporates simple random allocation for treatment assignment. Hence, simulated EVD + rt-PA is a random coin flip with a 50% chance of receiving rt-PA.

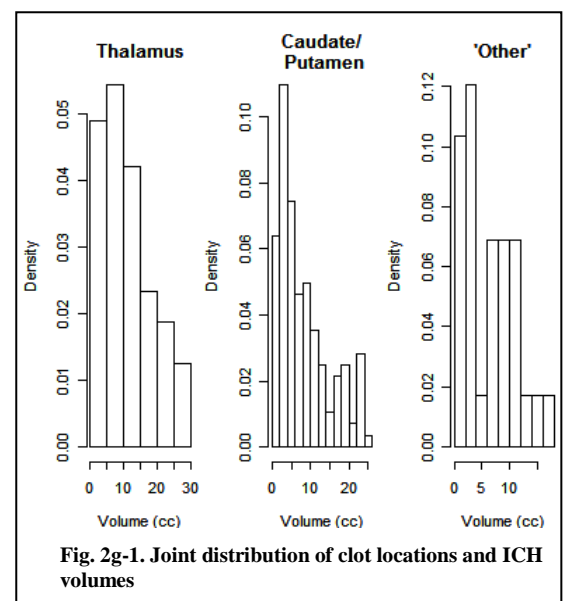


Fig. 2g-1. Joint distribution of clot locations and ICH volumes

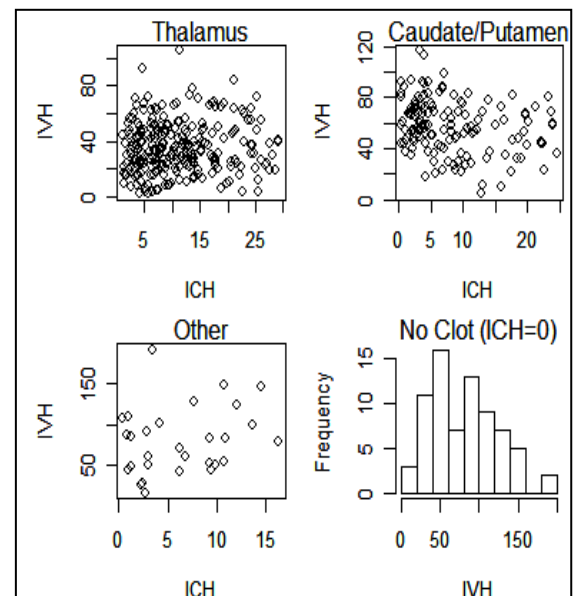
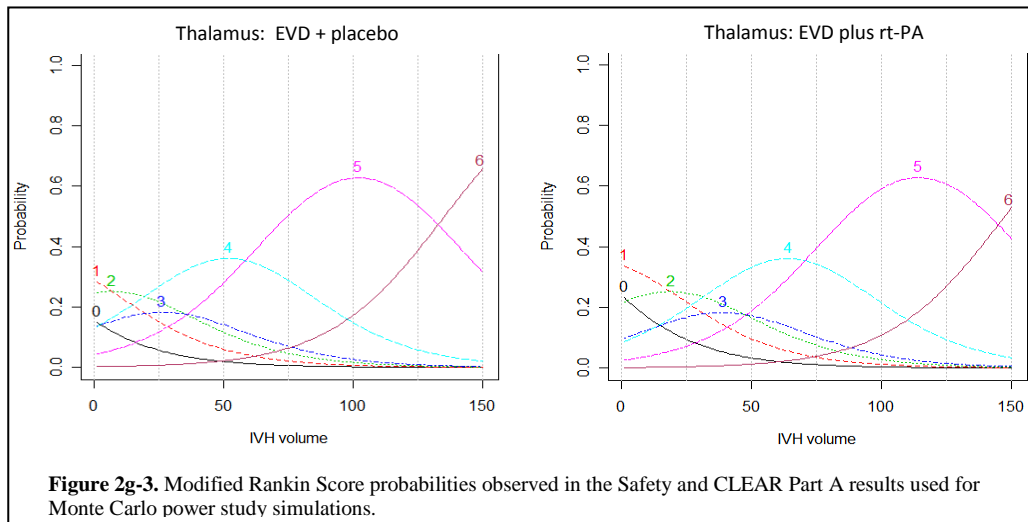


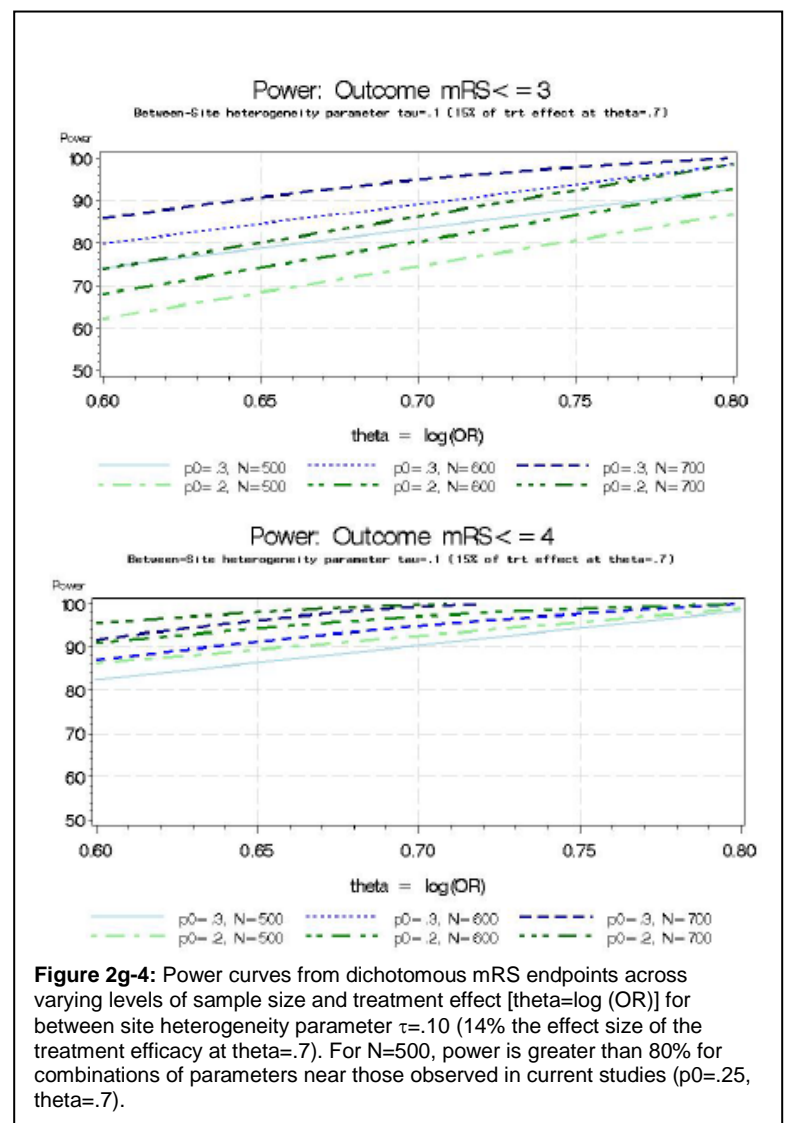
Fig. 2g-2. Joint plots of IVH, ICH volumes and clot location relationships



2.90,  $a_5 = 5.95$  were used; for a control rate approximately = 0.30, intercepts  $a_0 = -0.5$ ,  $a_1 = 0.2$ ,  $a_2 = 0.75$ ,  $a_3 = 1.5$ ,  $a_4 = 3.04$ ,  $a_5 = 5.55$  were used. Additionally, site clustering or between-site heterogeneity was parameterized as a latent effect with standard deviation  $\tau = .1$  and  $.25$ , assuming approximately 50 sites. These values lead to probability curves as depicted in Figure 2g-3, which shows the likelihood of attaining each mRS outcome across IVH volumes for the Thalamus clot location. The numbers directly above the probability curves denote the respective mRS score. Note that our observed data from the Safety and CLEAR part A study yields all seven probability curves shifted to the right under the EVD + rt-PA intervention, yielding higher success probabilities for lower (better) mRS outcomes. Given a subject's simulated clot location, ICH volume, IVH volume and treatment assignment, mRS outcome scores may then be drawn from a multinomial distribution with probabilities following these empirically observed relationships.

If we use this technique to draw a sample of mRS outcomes of size  $N=500$  (proposed trial size), we inherently simulate one possible outcome of the proposed trial. Following the five steps in this simulation procedure a large number of times, such as 1000, analyzing the resulting datasets each time and recording whether we obtain statistically significant treatment effect results at the 5% level leads to Monte Carlo estimates of the proposed trial's power to detect a treatment difference. Using this machinery, a variety of simulation scenarios were examined to judge the sensitivity of power towards sample size ( $N=500, 600$  &  $700$ ), effect size (odds-ratio = 1.8 to 2.2), control group outcome rates (placebo rates of good outcome  $mRS \leq 3 = 20\%, 30\%$ ), model choice (correctly specified vs. non-correctly specified model), and site clustering (between site heterogeneity parameterized as a latent effect with standard deviation  $\tau = .10$  and  $.25$  [i.e. 14% and 36% of log-odds-ratio treatment effect  $\theta = .7$ , (OR = 2.0), respectively]). Figure 2g-4 shows the power across varying levels of sample size and treatment efficacy parameter  $\theta = \log(OR)$  with a between site heterogeneity parameter  $\tau = .10$ , for both dichotomized outcomes  $mRS \leq 3$  and  $mRS \leq 4$ .  $P_0$  represents the proportion of patients in the EVD + placebo

**Step 5: Simulate the mRankin outcomes based on the rt-PA assignment, IVH & ICH volumes and clot location.** Parameter estimates for the categorical mRS outcomes observed in the Safety, CLEAR part A and part B studies were as follows: treatment effect:  $\theta = 0.6$  to  $0.8$  (i.e. odds-ratio of 1.8 to 2.2); IVH volume:  $b_1 = -0.043$ ; ICH volume  $b_2 = -0.097$ ; Clot Location: Thalamus:  $b_3 = -0.83$ ; Caudate/Putamen:  $b_4 = 1.01$ ; No Measurable Clot:  $b_5 = -0.82$ . For a control rate ( $p_0$ ) approximately = 0.20, intercepts  $a_0 = -0.1$ ,  $a_1 = 0.05$ ,  $a_2 = 0.25$ ,  $a_3 = 0.65$ ,  $a_4 =$



group with good outcomes ( $mRS \leq 3$  or  $mRS \leq 4$ ).

Hence, the proposed sample size of  $N=500$  adequately powers the trial to detect treatment effects around our previously observed treatment effect; clot removal with EVD + rt-PA resulting in a doubling of the odds of having a better mRS outcome when controlling for IVH and ICH volume and clot location. This corresponds with being able to determine an absolute difference of 15% or more in the probability of better outcomes comparing EVD + rt-PA and EVD + placebo groups, as specified in our primary hypothesis. Given our experience in controlling rebleeding and maximizing clot removal in the more recent CLEAR A and B studies, we expect the previously observed measure of  $\theta = 0.7$  ( $OR = 2.0$ ) to be a conservative estimate of the treatment effect.

Additional simulations were performed to examine sensitivity towards effects of a potential latent patient-severity factor based on an IVH volume  $> 60$  cc. Inclusion of this factor in the simulation methodology did not change the overall power results.

<b>Table 2g-1. Power Available to Detect Specified Effect With Alpha = 0.05 For Two Groups of Size 250 (Total of 500 patients)</b>				
Proportion with Good Outcome in the EVD + placebo Management Group				
Effect size (Abs diff.)	20%	25%	30%	35%
25%	>.99	>.99	>.99	>.99
20%	>.99	>.99	>.99	>.99
15%	.96	.94	.92	.91
14%	.93	.91	.88	.87
13%	.89	.86	.84	.82
12%	.84	.80	.77	.75
11%	.78	.73	.70	.68
10%	.70	.65	.61	.59

In addition to the Monte Carlo simulations above, we may investigate power for the primary Hypothesis for a study designed to enroll a total of 500 patients through standard rate comparison power formulae. The power available to detect various effect sizes is shown below for ranges between 20% to 35% of the current EVD + placebo group achieving a good outcome (such as mRS score  $\leq 3$ ) calculated using the normal approximation with continuity correction for a two sample test of equality of proportions (Table 2g-1).

**2g.1.2. Statistical Power - Primary Endpoint 2 (Modified Rankin Scale as Ordinal Score at 180 days).** Clot removal with EVD and treatment with low-dose rt-PA for IVH clot removal produces improved

outcome(s) assessed by the ordinal mRS when compared to EVD + placebo (Fleiss, Statistical methods for rates and proportions, New York: John Wiley & Sons, Inc.; 1981). The power to detect difference between treatment groups may be enhanced by retaining the ordinal nature of the mRS, hence we expect greater than 85% power as in the simulations detailed above. Binomial exact 95% confidence intervals for groups of 50, 125 and 250 patients for event rates ranging from 0.05 to 0.50 are shown in Table 2g-2. In terms of detecting differences in adverse event rates between the two groups, the study has 80% power, or better, to detect an increase of 0.125 in the rate of any event among the rt-PA treated patients provided the rate of that event experienced by patients who received EVD + placebo is at least 0.10. For example, if the bleeding or infection rate is 0.15 (15%) in the EVD + placebo group, the study has 80% power or better to detect a difference between the groups if the rate in the rt-PA group is 0.275 (27.5%) or higher.

**2g.1.3. Statistical Power - Primary Endpoint 3 (Modified Rankin Scale  $\leq 4$  at 180 days).** EVD and treatment with low-dose rt-PA for IVH clot removal produces improved outcome(s) using an alternate mRS cutoff at 180 days of  $mRS \leq 4$ . Power for primary endpoint 3 was examined similarly to that for the primary endpoint 1. As in Figure 2g-4, there was greater than 80% power to detect  $mRS \leq 4$  in all situations examined in the Monte Carlo simulations.

<b>Table 2g-2. Confidence intervals for event rates</b>			
Event Rate *	95% Confidence Interval Around Event Rate for		
	50 patients	125 patients	250 patients
.05	.013 -.165	.018 -.102	.025 -.082
.10	.033 -.218	.056 -.171	.066 -.144
.15	.072 -.291	.094 -.227	.106 -.198
.20	.100 -.337	.134 -.281	.152 -.255
.25	.146 -.403	.175 -.333	.196 -.306
.30	.179 -.446	.225 -.393	.244 -.361
.35	.229 -.508	.269 -.442	.289 -.411
.40	.264 -.548	.313 -.491	.339 -.464
.45	.318 -.607	.359 -.540	.385 -.512
.50	.355 -.645	.413 -.595	.436 -.564
* Or closest rate to this achievable with an integer number of events			

### 3. Figures

#### 3a. Figure S1. CT images correlating to different IVH volumes.

Volumetric software (Osirix) was used to measure clot volume by outlining and totaling each region of interest (IVH, ICH, catheter tract, and other areas of bleeding). The images presented here are representative of the sub groups of IVH volume used for adaptive randomization (<20 mL, 20-50 mL, >50 mL).

ICH: 0 cc  
IVH: 8.3 cc



ICH: 7.17 cc  
IVH: 18.3 cc



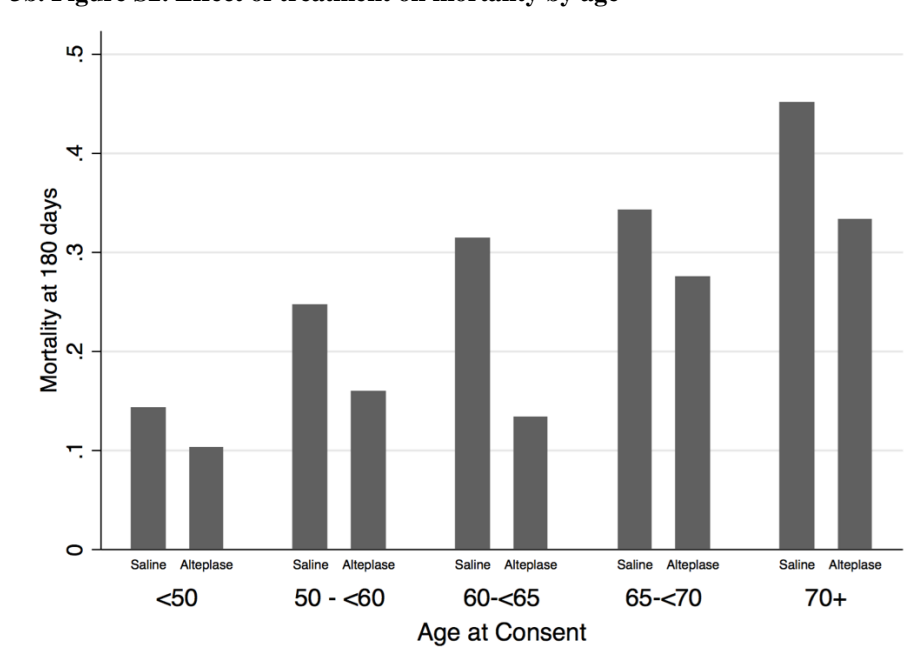
ICH: 6.3 cc  
IVH: 32.6 cc



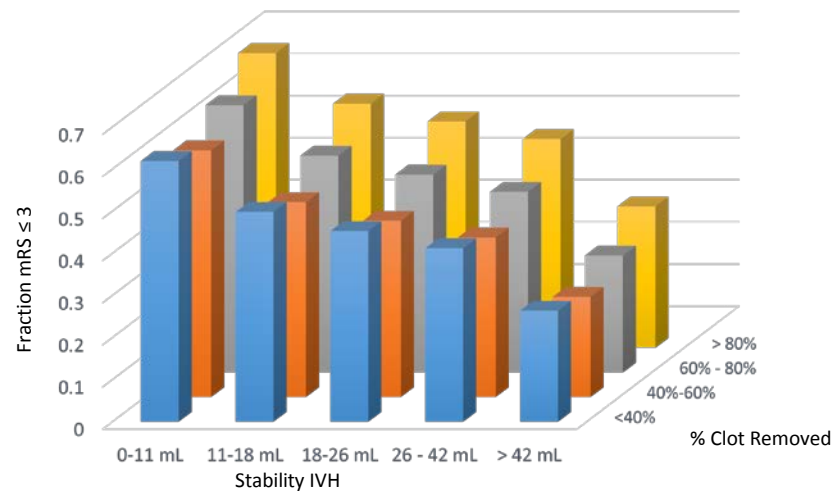
ICH: 1.31 cc  
IVH: 52.2 cc



**3b. Figure S2. Effect of treatment on mortality by age**



**3c. Figure S3. Relationship between mRS 0-3 and percent clot removed by IVH volume as determined at stability prior to randomization.**



#### 4. Tables

4a. Table S1. Primary and secondary analyses descriptive listing and corresponding results.

	Analyses	Results	Notes	Interpretation
<b>Primary Outcomes</b>				
1.1. 180 day mRS* (0-3)				
Univariate Treatment	Chi-Square Test	Alt: 47.6%, Sal: 44.9%. Risk Diff (95% CI) = 2.7% (-6.2%, 11.5%), p = 0.554		
Adjusted for IVH/ Thalamus	Wt-effect Across 6 Strata	Risk Diff (95% CI) = 3.5% (-4.2%, 11.9%)		
Full Adjustment	Multivariable Logit Model	Adj OR (95% CI) = 1.18 (0.75, 1.87), p = 0.465 Adj OR for mRS ≤ 3 v. > 3; Alt v. Sal.	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	No difference by random grp for mRS 0-3 proportion
1.2. mRS* as Ordinal Score	Unadj Prop Odds Model	OR (95% CI) = 0.81 (0.60, 1.11), p = 0.198 OR for mRS > K v. ≤ K; Alt v. Sal.	Null hypothesis of prop odds rejected; chi2 p = 0.025*	
	Adjust Prop Odds Model	Adj OR (95% CI) = 0.73 (0.53, 1.01), p = 0.060 Adj OR for mRS > K v. ≤ K; Alt v. Sal.	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)*	
			Null hypothesis of prop odds rejected; chi2 p = 0.018	
	Unadj Gen Ordered Logit Model for Ordered Data	OR (95% CI) = 0.90 (0.66, 1.24), p = 0.538 OR for mRS > K v. ≤ K if K = 1 - 4; Alt v. Sal.	Prop Odds satisfied for mRS 0, 1 - 4 assumed identical (chi 2 p=0.9967).*	
		OR (95% CI) = 0.55 (0.37, 0.81), p = 0.003 OR for mRS > 5 v. ≤ 5; Alt v. Sal.	Prop Odds satisfied for mRS 0, 1 - 4 assumed identical (chi 2 p=0.9967).*	Mortality less with random assignment to alteplase
	Adjust Gen Ordered Logit Model #1 for Ordered Data	Adj OR (95% CI) = 0.86 (0.62, 1.20), p = 0.380 Adj OR for mRS > K v. ≤ K if K = 1 - 4; Alt v. Sal.	Adj for Thal and Stab IVH (cat)*	
		Adj OR (95% CI) = 0.49 (0.32, 0.73), p = 0.0006 Adj OR for mRS > 5 v. ≤ 5; Alt v. Sal.	Adj for Thal and Stab IVH (cat)*	Mortality less with random assignment to alteplase
	Adjust Gen Ordered Logit Model #2 for Ordered Data	Adj OR (95% CI) = 0.89 (0.63, 1.25), p = 0.484 Adj OR for mRS > K v. ≤ K if K = 1 - 4; Alt v. Sal.	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)*	
		Adj OR (95% CI) = 0.44 (0.28, 0.71), p = 0.0003 Adj OR for mRS > 5 v. ≤ 5; Alt v. Sal.	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)*	Mortality less with random assignment to alteplase
1.3. 180 day mRS* (0-4)				
Univariate Treatment	Chi-Square Test	Alt: 64.2%, Sal: 61.6% Risk Diff (95% CI) = 2.6% (-5.9%, 11.1%), p = 0.552		
Full Adjustment	Multivariable Logit Model	Adj OR (95% CI) = 1.23 (0.80, 1.90), p = 0.350 OR for mRS ≤ 3 v. > 3; Alt v. Sal.	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	
1.4. Random Effects (mRS* 0-3)	Random Effects Model w/ site as random effect	OR (95% CI) = 1.11 (0.81, 1.53), p = 0.514 OR for good outcome Alt v. Sal. ICC = 1.3 X 10 <sup>-6</sup>	Unadjusted	No differences of mRS 0-3 attributable to site differences
	Adj Random Effects Model w/ site as random effect	Adj OR (95% CI) = 1.18 (0.78, 1.80), p = 0.428 OR for good outcome Alt v. Sal. ICC = 2.9 X 10 <sup>-7</sup>	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	

	Analyses	Results	Notes	Interpretation
1.5. Longitudinal (mRS* 0-3)	Uadj GEE model (Logit mRS (0-3) at 30 and 180 days)	30 Days: OR (95% CI) = 1.34 (0.85, 2.12) p = 0.207 180 Days: OR (95% CI) = 1.10 (0.77, 1.57) p = 0.597		No between grp differences mRS 0-3 over time
	Adj GEE model (Logit mRS (0-3) at 30 and 180 days)	30 Days: OR (95% CI) = 1.26 (0.75, 2.10) p = 0.384 180 Days: OR (95% CI) = 1.01 (0.62, 1.64) p = 0.964	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	
<b>Secondary Outcomes</b>				
2.1 All-Cause Mortality - 180 days	Log Rank Test	Mortality - Alt: 18.5%, Sal: 29.1%. P = 0.0056		Less mortality with random assignment to alteplase
2.2. Clot Removal	AUC / Logit Model	Adj OR (95% CI) = 0.96 (0.94, 0.97), p < 0.0001 Adj OR for mRS (0-3) per time-wt mL.	Adj for Trt, Age, GCS, Thal, Stab ICH	Greater clot removal associated with greater likelihood for mRS 0-3
IVH by Trt Interaction	Multivariable Logit Model	IVH < 20 mL – Adj OR (95% CI) = 0.69 (0.35, 1.38), p = 0.297 Adj OR for mRS <= 3 Alt v. Sal.	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	
		IVH >= 20 mL Adj OR (95% CI) = 1.91 (1.04, 3.52), p = 0.037 Adj OR for mRS <= 3 Alt v. Sal.		Per protocol analysis: greater mRS 0-3 in key randomized subgroup with assignment to alteplase
80% of Clot Removed	Multivariable Logit Model	Adj OR (95% CI) = 1.38 (0.82, 2.33), p = 0.226. Adj OR for mRS (0-3) for >80% v. <= 80% Clot Removed	Adj for Age, GCS, Thal, Stab IVH (cat)	
85% of Clot Removed	Multivariable Logit Model	Adj OR (95% CI) = 1.91 (1.03, 3.55), p = 0.040 Adj OR for mRS (0-3) for >85 % v. <= 85% Clot Removed	Adj for Age, GCS, Thal, Stab IVH (cat)	Threshold analysis- Post hoc- justified given finding of relationship to removal
90% of Clot Removed	Multivariable Logit Model	Adj OR (95% CI) = 2.25 (1.10, 4.58), p = 0.026 Adj OR for mRS (0-3) for >90% v. <= 90% Clot Removed	Adj for Age, GCS, Thal, Stab IVH (cat)	Threshold analysis- Post hoc- Justified given finding of relationship to removal
2.3. Critical Care Management	Rank Sum for skewed data (instead of linear regression), Chi-Square Test (in place of univariate logistic model)			
Hosp Days		Median (IQR) - Alt: 23 (17,31) days, Sal: 24 (16,31), p = 0.771		
ICU Days		Median (IQR) - Alt: 14 (11,21) days, Sal: 15 (12, 22), p = 0.098	Alt: 15 (12,22), Sal: 16 (13, 23), p=0.23	
Critical Care Complications				
ICP Management	Generalized Linear Models	Mean proportion of events of ICP >20mmHg – Alt: 9.8 mmHg, Sal: 10.2 mmHg, p = 0.450	Mean of patient-specific proportions	

	Analyses	Results	Notes	Interpretation
Mechanical ventilation		Alt: 73.9%, Sal: 76.5%, p=0.501		
Pressors		Alt: 24%:Sal: 25%, p=0.795		
Use of Shunts		Alt: 18.5%, Sal: 17.5%, p=0.784		
All infections Day 30 (SR)		Alt: 48.2%, Sal: 50.6%, p=0.592		
pneumonia day 30		Alt: 26.1%, Sal: 32.7%, p=0.105		
All infections Day 180 (SR)		Alt: 49.8%, Sal: 56.2%, p=0.152		
2.4. 30-Day Mortality / Safety	Fisher's Exact Test (was used instead of univariate logistic model due to small cell size)			
Mortality w/in 30 days		Alt: 8.8%, Sal: 14.3%. Risk Diff (95% CI) = -5.5% (-11.1%, 0.08%), p = 0.055	Bar Plot in ISC Slides (Hanley Talk). Email 2/9/16	
Bacterial Brain Infections		Alt: 6.8%, Sal: 10.4%. Risk Diff (95% CI) = -3.5% (-8.4%, 1.4%), p = 0.202		
Systematic Bleeds w/ 72 hours		Alt: 2.4%, Sal: 2.0%. Risk Diff (95% CI) = 0.42% (-2.2%, 3.0%), p =0.771		
Systematic Bleeds w/ 30 days		Alt: 3.6%, Sal: 3.2%. Risk Diff (95% CI) = 0.43% (-2.8%, 3.6%), p =0.811		
2.5. AE / SAE	Fisher's Exact Test (was used instead of univariate logistic model due to small cell size)	Alt: 45.8%, Sal: 60.2%. Risk Diff (95% CI) = -14.4% (-23.12%, -5.71%), p = 0.002		Fewer subject with SAEs in the alteplase grp
Brain infections day 180 (SR)		Alt: 7%, Sal: 12%, p=0.048		Fewer brain infections at 180 days in the alteplase grp
2.6. Predictors of Mortality	Unadjusted Cox Proportional Hazards Model	HR (95% CI) = 0.60 (0.41, 0.86), p = 0.006; Alt v. Sal		Model shows random assignment to alteplase associated with lower mortality
	Adjusted Cox Proportional Hazards Model	Adj HR (95% CI) = 0.58 (0.39, 0.85), p = 0.005; Alt v. Sal	Adj for Age, GCS, Thal, Stab ICH, Stab IVH	Adjusted model shows random assignment to alteplase associated with lower mortality
2.7. Sub-Group Analyses	Chi-Square Test - Difference in mRS 0-3 proportion			
Race (AA)		AA - Alt: 54.4%, Sal: 48.0%. Risk Diff (95% CI) = 6.4% (-8.8%, 21.7%), p = 0.410	N = 165	
Race (White)		White - Alt: 43.4%, Sal: 41.8%. Risk Diff (95% CI) = 1.6% (-9.6%, 12.8%), p = 0.781	N = 301	

	Analyses	Results	Notes	Interpretation
Gender(Female)		Female - Alt: 47.6%, Sal: 45.6%. Risk Diff (95% CI) = 2.0% (-11.3%, 15.2%), p = 0.773	N = 217	
Gender (Male)		Male - Alt: 47.6%, Sal: 44.3%. Risk Diff (95% CI) = 3.2% (-8.5%, 15.1%), p = 0.587	N = 274	
Age (<= 65 yr)		<= 65 - Alt: 53.6%, Sal: 52.1%. Risk Diff (95% CI) = 1.5% (-9.0%, 12.1%), p = 0.775	N = 346	
Age (> 65 yr)		> 65 - Alt: 31.3%, Sal: 29.5%. Risk Diff (95% CI) = 1.9% (-13.2%, 16.9%), p = 0.808	N = 145	
IVH (≤20 mL)		< 20 - Alt: 55.1%, Sal: 58.3%. Risk Diff (95% CI) = -3.3% (-16.5%, 9.9%), p = 0.625	N = 217	
IVH (20 - 50mL)		20 - 50 - Alt: 47.3%, Sal: 38.5%. Risk Diff (95% CI) = 8.7% (-4.3%, 21.8%), p = 0.191	N = 219	
IVH (> 50 mL)		> 50 - Alt: 18.5%, Sal: 17.9%. Risk Diff (95% CI) = 0.66% (-19.7%, 21.1%), p = 0.949	N = 55	
Location (Thalamic)		Thalamic - Alt: 38.8%, Sal: 37.4%. Risk Diff (95% CI) = 1.4% (-9.8%, 12.6%), p = 0.812	N = 286	
Location (Non-Thalamic)		Non-Thalamic - Alt: 60.6%, Sal: 54.7%. Risk Diff (95% CI) = 5.9% (-7.6%, 19.4%), p = 0.394	N = 205	
Severity Index	Regression of Treatment by subject severity level	Adj OR (95% CI) = 0.37 (0.31, 0.44), p < 0.0001. Odds for mRS 0-3 decreases for each unit increase in severity score	Severity score includes age, GCS, Thalamic location, Stab IVH, Stab ICH.	Assignment to alteplase did not improve mRS but did improve mortality (See Suppl section 2d.)
2.8. Functional Status				
NIHSS <sup>†</sup>	Rank Sum	Mean (SD) - Alt: 5.0 (7.0), Sal: 6.1 (7.9), p = 0.140	N (Alt) = 182, N (Sal) = 158	
Barthel <sup>‡</sup>	Rank Sum	Mean (SD) - Alt: 65.2 (37.7), Sal: 69.5 (35.1), p = 0.312	N (Alt) = 197, N (Sal) = 170	
eGOS <sup>§</sup> (>= Up SD v. <= Low SD)	Chi-Square Test	Alt: 39.4%, Sal: 32.0%. Risk Diff (95% CI) = 7.5% (-1.1%, 16.0%), p = 0.087		
eGOS <sup>§</sup> (>= Up SD v. <= Low SD)	Multivariable Logit Model	Adj OR (95% CI) = 1.54 (0.98, 2.43), p = 0.064 Adj OR for >= Up SD v. Low SD; Alt v. Sal.	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	
eGOS <sup>§</sup> ordinal	Generalized Ordinal Model Test of Proportionality unadjusted eGOS (chi 2 p = 0.306 for Prop Odds)	OR (95% CI) = 0.67 (0.48, 0.93), p = 0.016 OR for eGOS > K v. <= K; Alt v. Sal.	Reverse coded: 5 - death, 4 - VS+low SD, 3 - up SD, 2 - MD, 1 - GR	Proportional shift favors alteplase when all levels of eGOS considered.
eGOS <sup>§</sup> ordinal	Adjust Gen Ordered Logit Model for Ordered Data	Adj OR (95% CI) = 1.42 (0.70, 2.89), p = 0.336 Adj OR for eGOS MD or worse v. GR; Alt v. Sal.	Reverse coded: 5 - death, 4 - VS+low SD, 3 - up SD, 2 - MD, 1 - GR	
		Adj OR (95% CI) = 0.93 (0.57, 1.52), p = 0.783 Adj OR for eGOS Up SD or worse v. MD + GR.; Alt v. Sal.	Partial Proportional Odds Model: GR (low + up) and MD (low + up) identical	
	Test of proportionality, (VS+low SD), and MD, GR assumed identical (chi 2 p=0.080).	Adj OR (95% CI) = 0.61 (0.39, 0.94), p = 0.025 Adj OR for eGOS (VS+low SD) + Death v. Up SD + MD+ GR; Alt v. Sal.		eGOS identifies groups different for VS, low SD, and mortality
		Adj OR (95% CI) = 0.47 (0.29, 0.75), p = 0.002 Adj OR for eGOS Death v. (VS+ low SD) + Up SD + MD + GR.; Alt v. Sal.		eGOS identifies groups different for mortality
2.9. QoL	T-test			QoL not different by Grp
SIS <sup>‡</sup> (Strength)		Mean - Alt: 55.0, Sal: 58.8, p = 0.312		

	Analyses	Results	Notes	Interpretation
SIS <sup>†</sup> (Mobility)		Mean - Alt: 58.3, Sal: 60.1, p = 0.652		
SIS <sup>†</sup> (Hand Function)		Mean - Alt: 53.4, Sal: 56.5, p = 0.478		
SIS <sup>†</sup> (ADL)		Mean - Alt: 59.3, Sal: 61.2, p = 0.634		
SIS <sup>†</sup> (Communication)		Mean - Alt: 76.0, Sal: 79.6, p = 0.255		
SIS <sup>†</sup> (Thinking)		Mean - Alt: 58.5, Sal: 62.7, p = 0.224		
SIS <sup>†</sup> (Emotion)		Mean - Alt: 73.1, Sal: 73.5, p = 0.882		
SIS <sup>†</sup> (Participation)		Mean - Alt: 47.5, Sal: 49.6, p = 0.551		
EuroQol Vas <sup>§</sup>		Mean (SD) - Alt: 62.8 (26.0), Sal: 65.1 (23.3), p = 0.376		
	Accept Null			
	p<0.05 – <b>Reject Null</b>			

\*Scores on the modified Rankin Scale (mRS) range from 0 (no disability) to 5 (severe disability) to 6 (death); for ordinal analysis, mRS 0 and 1 combined

†Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 (no disability) to 42 (severe disability)

‡Scores on the Barthel Index (BI) range from 0 (unable to perform any) to 100 (able to perform all) activities of daily living

§Scores on the Extended Glasgow Outcome Scale (eGOS) range upper good recovery to death

†Scores on the Stroke Impact Scale (SIS) range from 1 (most impaired) to 5 (no impairment) on 16 activity domains

¶Scores on the EuroQol Visual Analog Scale (EQ-VAS) range from 0 (worst) to 100 (best) imaginable health state

4b. Table S2. eGOS score frequencies for the 30, 180, and 365 day time points.

eGOS	Visit and Treatment							
	30 days				180 days			
	Saline	Alteplase	Saline	Alteplase	Saline	Alteplase	Saline	Alteplase
Upper GR	4	1.62	3	1.23	17	7.05	15	6.22
Lower GR	4	1.62	1	0.41	5	2.07	6	2.49
Upper MD	2	0.81	10	4.12	12	4.98	13	5.39
Lower MD	4	1.62	9	3.70	10	4.15	19	7.88
Upper SD	19	7.69	19	7.82	33	13.69	42	17.43
Lower SD	132	53.44	138	56.79	85	35.27	92	38.17
VS	46	18.62	41	16.87	6	2.49	8	3.32
Dead	36	14.57	22	9.05	73	30.29	46	19.09
Totals	247	100.0	243	100.0	241	100.0	241	100.0

4c. Table S3. Univariable and Multivariable Analyses of Dichotomized mRS Modified Rankin Scale (mRS) Score at Day 180 (mRS 0-3 vs. 4-6); Illustrating the Influences of Treatment (alteplase vs. saline), Several Disease Factors, and Effect of Clot Removal on mRS score at Day 180 Outcome.

Variables	Univariable (Unadjusted) Models OR <sup>2</sup> [95% CI]	Multivariable Model 1 (All Patients) AOR <sup>3</sup> [95% CI]	Multivariable Model 2 (Treatment by IVH interaction at 20 mL) <sup>4</sup> AOR [95% CI]
Age (per year increase)	0.94* [0.93, 0.96]	0.95* [0.93, 0.97]	0.94* [0.92, 0.96]
Randomization GCS <sup>†</sup> (per unit increase)	1.27* [1.20, 1.36]	1.21* [1.13, 1.30]	1.21* [1.12, 1.30]
ICH Location (Thalamic v. Other)	0.45* [0.31, 0.65]	0.46*** [0.26, 0.83]	0.44** [0.24, 0.80]
Stability ICH (per mL)	0.90* [0.87, 0.92]	0.90* [0.87, 0.93]	0.89* [0.86, 0.93]
AUC normalized (per mL of time-weighted clot volume remaining)	0.96* [0.95, 0.98]	0.96* [0.94, 0.97]	
Treatment – All Patients (rt-PA v. saline)	1.11 [0.78, 1.59]	0.93 [0.59, 1.45]	
Treatment – IVH > 20 mL (alteplase vs. saline)	1.36 [0.84, 2.23]		1.91*** [1.04, 3.52]

<sup>1</sup> Model also adjusts for stability IVH; <sup>2</sup> OR: odds ratio; <sup>3</sup> AOR: adjusted odds ratio

<sup>†</sup> Scores on the Glasgow Coma Scale (GCS) range from 15 (fully conscious) to 3 (deep coma)

\*p < 0.001; \*\*p < 0.01; \*\*\*p < 0.05

**4d. Table S4. Additional outcome variables by group.**

Outcome Variables	Alteplase (N=249)	Saline (N=251)	p-value
eGOS <sup>§</sup> ≥ Upper SD at 180 days: no. (%)	95 (39)	77 (32)	0.087
Time to Home <sup>†</sup> : Median (25 <sup>th</sup> percentile)	95 (42)	107 (50)	0.771
Location at D180: no. (%)	249 (100)	251 (100)	0.062
Home: no. (%)	138 (55)	124 (49)	
Rehab Unit: no. (%)	27 (11)	18 (7)	
Acute: no. (%)	4 (2)	5 (2)	
Long-Term Care Facility: no. (%)	34 (14)	29 (12)	
Dead: no. (%)	46 (18)	73 (29)	
Missing: no. (%)	0 (0)	2 (1)	
EuroQoL Visual Analog Scale (EQ-VAS) <sup>¶</sup> : Median [IQR]	70 [50, 80]	70 [50, 80]	0.497
Barthel Index (BI) <sup>[1]</sup> : Median [IQR]	85 [30, 100]	85 [45, 100]	0.312

<sup>§</sup>Scores on the Extended Glasgow Outcome Scale (eGOS) range from upper good recovery to death

<sup>†</sup>25<sup>th</sup> percentile provided in place of IQR. Data censored at 180 days for analysis and 75% of subjects were not yet home.

<sup>¶</sup>Scores on the EuroQoL Visual Analog Scale (EQ-VAS) range from 0 (worst) to 100 (best) imaginable health state

<sup>[1]</sup>Scores on the Barthel Index (BI) range from 0 (unable to perform any) to 100 (able to perform all) activities of daily living

**4e. Table S5. Primary reason for exclusion by count and frequency.**

Primary Exclusion Criteria	Subject Count (n=9,784)	Frequency (%)
Structural etiology (aneurysm, Moyamoya, etc.)	1,312	13.4
Outside allowed age range	1,280	13.1
Lack of 3 <sup>rd</sup> /4 <sup>th</sup> obstruction	1,266	12.9
ICH volume greater than 30cc	1,250	12.8
No EVD placed	1,239	12.7
Infratentorial involvement	739	7.6
DNR status	347	3.6
Historic Rankin	158	1.6
Uncontrolled PTT, PLT, INR	157	1.6
Other Exclusion	2,036	20.7

**4f. Table S6. Demographics for screen failures vs. enrolled subjects.**

Demographic	Screen Failures (n=9,784)	Enrolled (n=500)	p-Value (Chi-Square w/Yates)
Gender			
Female	4,604 (47.1%)	222 (44.4%)	0.156
Male	5,138 (52.5%)	278 (55.6%)	
Unspecified	42 (0.4%)	0 (0.0%)	
Primary Diagnosis			
ICH with IVH	7,604 (77.7%)	428 (85.6%)	<0.00001
Primary IVH	1,286 (13.1%)	72 (14.4%)	
Unspecified	894 (9.1%)	0 (0.0%)	
Race			
White	6,624 (67.7%)	306 (61.2%)	<0.00001
African-American	1,762 (18.0%)	170 (34.0%)	
Asian	358 (3.7%)	14 (2.8%)	
Other/Unspecified	1040 (10.6%)	10 (2.0%)	

**4g. Table S7. Proximate causes of death.**

Proximate causes of death for subjects who died prior to 30 days and 30 or more days post symptom onset but prior to completing the day 180 visit.

Proximate Cause of Death	< 30 Days			30-180 Days			0-180 Days Combined
	Alteplase	Placebo	Total	Alteplase	Placebo	Total	Total
Neurologic no. (%)	17 (73.91)	26 (74.29)	43 (74.14)	7 (30.43)	13 (34.21)	20 (32.79)	63 (52.94)
Cardiac no. (%)	3 (13.04)	3 (8.57)	6 (10.34)	3 (13.04)	6 (15.79)	9 (14.75)	15 (12.61)
Respiratory no. (%)	2 (8.70)	2 (5.71)	4 (6.90)	3 (13.04)	8 (21.05)	11 (18.03)	15 (12.61)
Renal no. (%)	0 (0.00)	0 (0.00)	0 (0.00)	1 (4.35)	1 (2.63)	2 (3.28)	2 (1.68)
Gastrointestinal no. (%)	1 (4.35)	0 (0.00)	1 (1.72)	1 (4.35)	0 (0.00)	1 (1.64)	2 (1.68)
Infection, non-neurologic no. (%)	0 (0.00)	3 (8.57)	3 (5.17)	4 (17.39)	2 (5.26)	6 (9.84)	9 (7.56)
Unknown no. (%)	0 (0.00)	1 (2.86)	1 (21.52)	4 (17.39)	8 (21.05)	12 (19.67)	13 (10.92)
<b>Total no.</b>	<b>23</b>	<b>35</b>	<b>58</b>	<b>23</b>	<b>38</b>	<b>61</b>	<b>119</b>

**4h. Table S9. Premorbid, historical modified Rankin Scale scores by treatment group.**

Historical mRS*	Alteplase	Saline	Total
0 no. (%)	219 (50.1)	218 (49.9)	437 (100)
1 no. (%)	30 (48.4)	32 (51.6)	62 (100)
2 no. (%)	0 (0.0)	1 (100.0)	1 (100)
Total no. (%)	249 (49.8)	251 (50.2)	500 (100)

\*Scores on the modified Rankin Scale (mRS) range from 0 (no disability) to 5 (severe disability) to 6 (death)

**4i. Table S10. Effect of treatment on mortality by age (data from Figure S4 in tabular format)**

Treatment	5 Age Categories				
	<50	50 - <60	60-<65	65-<70	70+
Saline (n)	49	81	35	35	51
Mortality %	14.0%	25.0%	31.0%	34.0%	45.0%
Alteplase(n)	58	75	45	29	42
Mortality %	10.0%	16.0%	13.0%	28.0%	33.0%

**4j. Table S11. Summary of Key Primary and Secondary Analyses and Results from Supplemental Table S1.**

<b>PRIMARY</b>				
			Saline – Alteplase Difference (95% CI)	
1.1	Functional Outcome	3% increase mRS 0-3	3 (-6, 12)	p=0.554
1.2 – 1.5	Alt. Analyses of mRS Levels	mRS 6 half as likely with alteplase	0.5 (0.3, 0.7)	p=0.0006
<b>KEY SECONDARY</b>				
2.1	180-day Mortality Outcome	11% decrease with alteplase	11 (3, 8)	p=0.007
2.2	Clot Removal	Associated with greater % mRS 0-3	---	p<0.0001
2.3	ICU Care	No difference		p=0.098
2.4	30-day Mortality/Safety	Trend favors alteplase		p=0.055
2.5	Safety-AEs/SAEs	14% fewer SAEs with alteplase 5% less ventriculitis @ 180 days with alteplase	-14 (-23, -6) -5 (10.7, 0.4)	p=0.002 p= 0.047
2.6	Predictors of Mortality	Adjusted hazard of death 0.58	0.6 (0.4, 0.9)	p=0.005
2.7	Sub-group	No differences		NS (all listed in Table S1)

## 5. REFERENCES

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